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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,707	01/11/2001	Ira H. Pastan	15280-3561US	3958

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EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	PAPER NUMBER
1645	15

DATE MAILED: 06/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/673,707	PASTAN ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,19-24 and 52-103* is/are pending in the application.

4a) Of the above claim(s) *19-24,59-67 and 79-103* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,52-58 and 68-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the separate inventions found by the Action share the same technical feature (i.e. scFv antibodies targeted to cells on which gp120 is targeted) hence share unity of invention. Additionally, Applicant asserts that the EPO decision not to object to the unity of invention under PCT Rule 1.32 reflects the correct application of said rule. This is not found persuasive because, contrary to Applicant's assertion, all inventions do not share the same technical feature. Minimally, the antibodies of group III and the nucleic acids encoding the same cannot be considered to share the same technical feature as the immunotoxins of group I merely because the former is a component of the latter With regard to the EPO decision not to object to the unity of invention, Applicant is reminded that each application is examined on its own merits and as such any decision made by the EPO has not bearing on said prosecution.

The requirement is still deemed proper and is therefore made FINAL.

The amendments filed on 8-13-2002, 12-13-2002 and 3-14-2003 are acknowledged. Claims 4, 61, 70, 81 and 92 have been amended. Claims 12-18 and 25-51 have been canceled. Claims 57-103 have been added. Claims 59-67 and 79-103 have been withdrawn from consideration as being drawn to non-elected inventions. Newly added claims 57-58 and 68-78 will be examined even though Applicant did not indicate that they read on the elected invention. In conclusion, claims 1-11, 19-24 and 52-103 are

pending. Claims 19-24, 59-67 and 79-103 have been withdrawn from consideration. Claims 1-11, 52-58 and 68-78 are currently under examination.

Information Disclosure Statement

The information disclosure statement filed on 1-16-2001 is acknowledged. An initialed copy is attached hereto.

Specification

The specification is objected to for the following reason(s):

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

The specification refers to U.S. patent Applications that have since been issued. For example, on page 8 the specification refers to U.S. Application 07/522,563 that has been issued as U.S. Patent 5,458,878. Applicant is directed to update the status of **all** recited applications.

The specification discloses that SEQ ID NO:1 is the sequence of both the intact 3b3 antibody and a 3b3(Fv) (for example, see page 16).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 10, 55-56, 58, 74, 76 and 78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that antibodies 3b3(Fv) and 3B3(dsFv) as well as immunotoxins 3B3(Fv)-PE38 and 3B3(dsFv)-PE38 are required in order to practice the invention. The deposit of biological material is considered by the Examiner to be necessary for the enablement of the current invention (see 37 CRF 1.808(a)). The rejected claims all recite said biological material in a manner suggesting they each constitute a single entity. Since the specification provides no sequences for said material and one of skill in the art would not be able to discern what V_H and V_L sequences of the 3B3 antibody are incorporated into the claimed 3B3(Fv) or 3B3(dsFv), deposit of the aforementioned biological material is required.

If the deposit is made under terms of the Budapest Treaty, then an affidavit or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty *and* that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit, or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

1) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

2) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent; and

3) the deposits will be maintained for a term of at least thirty (30) years from the date of the deposit or for the enforceable life of the patent or for a period of at least five (5) years after the most recent request for the furnishing of a sample of the deposited material, whichever is longest; and

4) a viability statement in accordance with the provisions of 37 CFR 1.807; and
5) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CRF 1.809(d) should be added to the specification. See 37 CFR 1.803 – 1.809 for additional explanation of these requirements.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 52-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 52 are rendered vague and indefinite by the use of the phrase "a minimum binding affinity of 3B3". It is unclear what is meant by said phrase. Is Applicant stating that the claimed antibody must have the minimum binding affinity of 3B3 to gp120 or some other antigen? If the latter is true, what antigen? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claim 57 is rendered vague and indefinite by the use of the term "FV("dsFv"). It is unclear what is meant by said term. Is Applicant referring to Fv(dsFv)?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11, 52-56 and 38-74 and 77-78 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Bera et al. (Molecular Medicine Vol. 4, 1998, pages 384-391).

The instant invention is drawn to immunotoxins comprising a cytotoxin (e.g. PE38) attached to an anti-gp120 antibody (e.g. 3B3) having the binding specificity of 3B3. Said antibody may be an Fv or an scFv. The instant invention is also drawn to kits and compositions comprising said immunotoxins.

Bera et al. disclose recombinant immunotoxins directed against the HIV-1 envelope protein. Said immunotoxin consisting of a single chain Fv of 3B3 fused to a truncated version of *Pseudomonas* exotoxin A (3B3{Fv}-PE38) (see abstract). Moreover, Bera et al. disclose that said 3B3(Fv)-PE38 has the same binding affinity of the parental Fab antibody (see abstract and the Binding Assays section on pages 385-386) and was suspended (dissolved) in a pharmaceutically acceptable carrier or excipient (e.g. PBS){see page (see page 86). The disclosure by Bera et al. differs from the instant invention in that they do not explicitly recite the incorporation of said immunotoxins in kits. However, said incorporation into kits would have been obvious to one of skill in the art in order to reduce cost and ease preparation time. Consequently, the disclosure by Bera et al. anticipates or renders obvious, all the limitations of the rejected claims.

It should be noted that the availability of the cited reference under 35 U.S.C. 102 is being determined. If it is determined that said reference was not publicly available before the claimed priority date of the instant invention, the aforementioned rejection will be withdrawn.

Claims 1-3, 6, 11, 57, 68-69, 72 and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsushita et al. (Aids Research and Human Retroviruses Vol. 6 No. 2, 1990, pages 193-203).

The instant invention is drawn to immunotoxins comprising a cytotoxin (e.g. PE) attached to an anti-gp120 antibody having the binding specificity of 3B3. Said antibody being a dsFv. The instant invention is also drawn to compositions comprising said immunotoxins.

Matsushita et al. disclose anti-pg120 immunotoxins comprising the 0.5β antibody coupled to the *Pseudomonas* exotoxin (see abstract). It should be noted that, in absence of evidence to the contrary, the 0.5β antibody is deemed to inherently have a binding affinity equal to or greater than that of the 3B3 antibody since they share the same specificity.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were

made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 57-58 and 75-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bera et al. (Molecular Medicine Vol. 4, 1998, pages 384-391) in view of Pastan et al. (U.S. Patent 6,147,203).

The instant invention is drawn to immunotoxins comprising a cytotoxin (e.g. PE38) attached to an anti-gp120 antibody (e.g. 3B3) having the binding specificity of 3B3. Said antibody is a dsFv. The instant invention is also drawn to kits and compositions comprising said immunotoxins.

Bera et al. disclose recombinant immunotoxins directed against the HIV-1 envelope protein. Said immunotoxin consisting of a single chain Fv of 3B3 fused to a truncated version of *Pseudomonas* exotoxin A [3B3(Fv)-PE38] (see abstract). Moreover, Bera et al. disclose that said 3B3(Fv)-PE38 has the same binding affinity of the parental Fab antibody (see abstract and the Binding Assays section on pages 385-386) and was suspended (dissolved) in a pharmaceutically acceptable carrier or excipient (e.g. PBS){see page (see page 86). The disclosure by Bera et al. differs from the instant invention in that they do not explicitly recite that the antibody used is a dsFv. Pastan et al. disclose Fv antibody fragments stabilized by a disulfide bond (dsFv). Moreover, Pastan et

al. disclose that said dsFv fragments can be used to make fusion proteins such as immunotoxins further comprising a cytotoxic agent (see column 9, lines 10-18). Pastan et al. further disclose that said cytotoxic agent could be ricin or *Pseudomonas* toxin A (see column 9, line 40). Consequently, it would have been obvious to one of skill in the art to use the procedures for producing dsFv immunotoxins as disclosed by Pastan et al. utilizing the 3B3 antibody and PE38 disclosed by Bera et al. to produce a 3B3(dsFv)-PE38 immunotoxin. One would have been motivated to combine said disclosures in order to take advantage of the increased maintenance of affinity afforded by the dsFv fusion molecules (see column 1, lines 61-62). One would have had a high expectation of success given that Pastan et al. disclose that their dsFv could be coupled with PE to produce immunotoxins.

It should be noted that the availability of the Bera et al. reference under 35 U.S.C. 102 is being determined. If it is determined that said reference was not publicly available before the claimed priority date of the instant invention, the aforementioned rejection will be withdrawn.

Claims 1-6, 8-9, 11, 52-55,57, 68-72 and 74-77 are rejected under 35 U.S.C. 103(a) as obvious over Matsushita et al. (Aids Research and Human Retroviruses Vol. 6 No. 2, 1990, pages 193-203) in view of Barbas et al. (PNAS Vol. 91, 1994, pages 3809-3813 – IDS-5) and Pastan et al. (U.S. Patent 5,458,878 – IDS-5).

Matsushita et al. disclose anti-pg120 immunotoxins comprising the 0.5β antibody coupled to the *Pseudomonas* exotoxin (see abstract). Matsushita et al. differs from the

instant invention in that they don't disclose the use of the 3B3 antibody or the use of altered PE40. Barbas et al. disclose a human antibody to gp120 (3B3) with broad strain cross-reactivity (see page 3812-3813). Pastan et al. disclose modifications of the carboxyl terminus of the PE molecule resulting in increased cytotoxicity (see abstract and column 3, line 27 to column 4, line 10). Given that Matsushita et al. suggest the use of an antibody that is broadly reactive with a number of HIV isolates (see page 200), it would have been obvious for one of ordinary skill in the art to use the 3B3 antibody in the immunotoxin disclosed by Matsushita et al. Moreover, it would a have been equally obvious for one of ordinary skill to incorporate the PE modifications disclosed by Pastan et al. in order to take advantage of the resulting increase in cytotoxicity. It should be noted that while the incorporation of immunotoxins in kits is not explicitly disclosed by Matsushita et al., said incorporation would have been obvious to one of ordinary skill in the art in order to reduce cost and ease preparation time.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Robert A. Zeman
June 5, 2003